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Epidemiology of Hantaan and Related Viruses

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Abstract | Hantaan and related viruses, the causative agents of hemorrhagic fever with renal syndrome (HFRS), are significant human pathogens. Current epidemiologic evidence indicates that these pathogens are distrubted more widely than once believed, and they are likely to cause disease when man comes into close contact with infected rodents. This report summarizes the characteristics of the Hantaanp-related viruses of the genus *Hantavirus* including epidemiology, ecological characteristics, routes of transmission, and mechanisms of virus maintenance.

Recent advances in our understanding of Hantaan and related viruses, the causative agents of hemorrhagic fever with renal syndrome (HFRS) (1), have demonstrated that members of this group of viruses are significant human pathogens whose potential to cause disease in man has yet to be fully recognized. While we are still learning the true extent of human disease due to this group of viruses, it is already clear that these agents are distributed much more widely than the traditionally recognized boundaries of classical HFRS would suggest (2). It now seems likely that human disease due to Hantaan-related viruses may be identified in many areas of the world where infected rodents come into close contact with man.

To date, four distinct groups of Hantaan-related viruses have been isolated and examined. These share antigenic and genetic characteristics and together comprise the newly proposed genus *Hantavirus* of the virus family Bunyaviridae (3-6). These agents also share similarities in their epidemiological and ecological characteristics, routes of transmission and mechanisms of virus maintenance. The objective of this report is to summarize these characteristics of the hantaviruses. Subsequent papers will describe their virological characteristics and the clinical disease which may follow infection of man (7,8).

Infection of rodents

Central to an understanding of the natural history of hantaviruses is recognition of the critical role played by rodents in virus maintenance and transmission. Hantaviruses cause chronic, apparently asymptomatic, infections of their rodent hosts (9-11). In this regard they are more like viruses of the family Arenaviridae, rather than the traditionally vectorborne Bunyaviridae (12,13). The typical time course of infection of a rodent by a hantavirus is depicted in Figure 1. Following infection, the suscep-

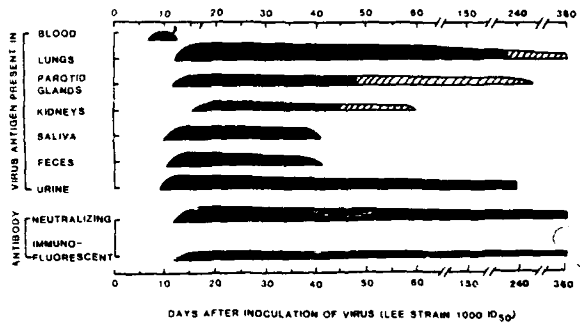

Figure 1 Viremia, persistence of virus and antigen (solid area), or antigen alone (shaded areas) in tissues, and duration of antibody following inoculation of *Apodemus agrarius* with Hantaan virus. Reprinted from Lee HW, Lee PW, Baek LJ *et al.* Intraspecific transmission of Hantaan virus, etiologic agent of Korean hemorrhagic fever, in the rodent *Apodemus agrarius*. *Am J Trop Med Hyg* 1981; 30:1106–12. Used by permission, The American Society of Tropical Medicine and Hygiene.

tible rodent is viremic for about a week. During the viremic phase, virus is disseminated throughout the body. After viremia, specific antigen is usually abundant in the hosts lungs, spleen and kidneys. Antigen expression persists in these organs for long periods, perhaps for the life of the rodent. An immune response occurs following viremia, which results in the production of humoral antibody detectable by both the indirect immunofluorescent antibody (IFA) assay and neutralization tests. These antibodies probably persist for the life of the host, but apparently do not diminish the abundance of antigen expressed in organs. At present, the role of antibody in regulating shedding of virus in urines, feces or saliva is incompletely understood. The duration and intensity of infectious virus shedding varies with host species and infecting virus, but in general, virus is shed for extended periods in these body fluids, and this is thought to be the source of most transmissible virus. Transmission to man is thought to occur primarily via aerosolized urine or feces,

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although incidental accounts of presumed transmission by rodent bite have been reported (14). Saliva-mediated transmission probably plays a more important role in horizontal passage of the virus between rodents, especially *Rattus*, where the duration and magnitude of virus shed in saliva appear to be greater. Preliminary results indicate that vertical transmission of hantaviruses probably does not occur (15). However, much more information is clearly needed to establish this with certainty. There is little to suggest that, unlike other viruses of the family Bunyaviridae, arthropods serve as important vectors of these viruses.

Korean hemorrhagic fever and *Apodemus agrarius*

The work of H.W. Lee and his colleagues in Seoul, Korea, represent the cornerstone of our understanding of hantaviruses. Lee and associates (16) first isolated Hantaan virus from the lungs of infected *Apodemus agrarius* mice captured in the region of Korea known to be endemic for Korean hemorrhagic fever (KHF) and demonstrated that this virus was the probably etiologic agent for KHF. The agent was named Hantaan virus after the river which transects the endemic zone. Later, the virus was adapted to growth in cell culture by French, *et al.* (17) and that resulted in the availability of the first serological test for epidemiological studies

As shown in Figure 2, two peaks of human disease occur in Korea, one in the spring and a larger one in the fall (11). Studies of this seasonablity in Korea found that time of increased virus transmission to man could be linked to increased prevalence of Hantaan virus in *Apodemus* mice. During these periods, *Apodemus* are reproductively active and spend more time outside their burrows.

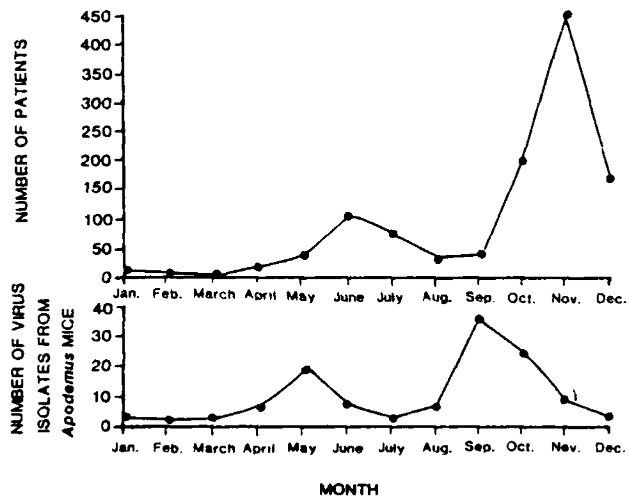

Figure 2 Cumulative seasonal prevalence of Korean hemorrhagic fever in man and of *Apodemus agrarius* infected with Hantaan virus in the endemic area of Kyunggi Province in Korea from 1975 to 1978. Reprinted from Lee HW. Korean hemorrhagic fever. *Prog Med Virol* 1982; 28:96–113. Used by permission, S. Karger AG, Basel.

In addition, gravid *Apodemus* excrete much more urine than non-gravid mice, so that more infectious virus is introduced into the environment. Simultaneously, farmers spend more time in their fields during the spring and fall, either planting or harvesting their crops. Also, environmental conditions are driest then, thus increasing the potential for aerosal transmission. Finally, *Apodemus* mice frequently seek shelter in houses, barns and other man-made structures in the fall as winter approaches. Collectively, these factors appear to contribute to the seasonal appearance of the disease in Korea. Similar situations probably exist in other endemic foci of the disease throughout much of Asia and the eastern Soviet Union, where similar or identical diseases occur under the rubrics of epidemic hemorrhage fever and others. (See Gajdusek, *et al.* (1984) for a complete list of synonyms.) The distribution of Hantaan virus is not known with certainty; however, its distribution in Asia it is likely to follow the distribution of its primary host, *Apodemus agarius*, which is shown in Figure 3 (19).

Hemorrhagic fever with renal syndrome and rats

As part of their studies on KHF, Lee and his colleagues also identified patients, infected with a "mild" form of HFRS, who resided in the urban centers of Korea, far from the recognized endemic region of KHF (20). The patients were city dwellers, people with no history of travel outside the city. When attempts were made to collect small rodents around patients' houses, no *Apodemus* could be found; however, domestic rats, both *Rattus rattus* and *R. norvegicus* were present. Captured rats were examined for virus infection and both Hantaan antigen and antibody were detected by IFA. It was concluded that domestic rats were the source of the human disease. Further study found that infection of domestic rats with Hantaan-like viruses was not an isolated occurrence, but rather a frequent observation in many areas of Korea. An especially significant observation was the finding of infected rats at Inchon, the major international port of Korea.

Following these observations, it was hypothesized that domestic rats infected with Hantaan, or a closely related virus, may have been disseminated worldwide through international shipping (20,21). To investigate this possibility, wharf rat populations were sampled at major international ports in the United States (21,22). We sampled ports in Philadelphia, Houston and several in California, and found rats abundant in Philadelphia and Houston, where food and harborage were both locally plentiful (21,23). When sera from captured rats were examined for antibody to Hantaan virus by IFA, positive rats were found clustered at discrete foci of infection, rather than uniformly distributed throughout the entire rodent populations.

Using tissues obtained from captured infected rats, several isolates of Hantaan-like virus were made. An isolate from Philadelphia and one from Houston were selected and compared to prototype Hantaan virus to deter-

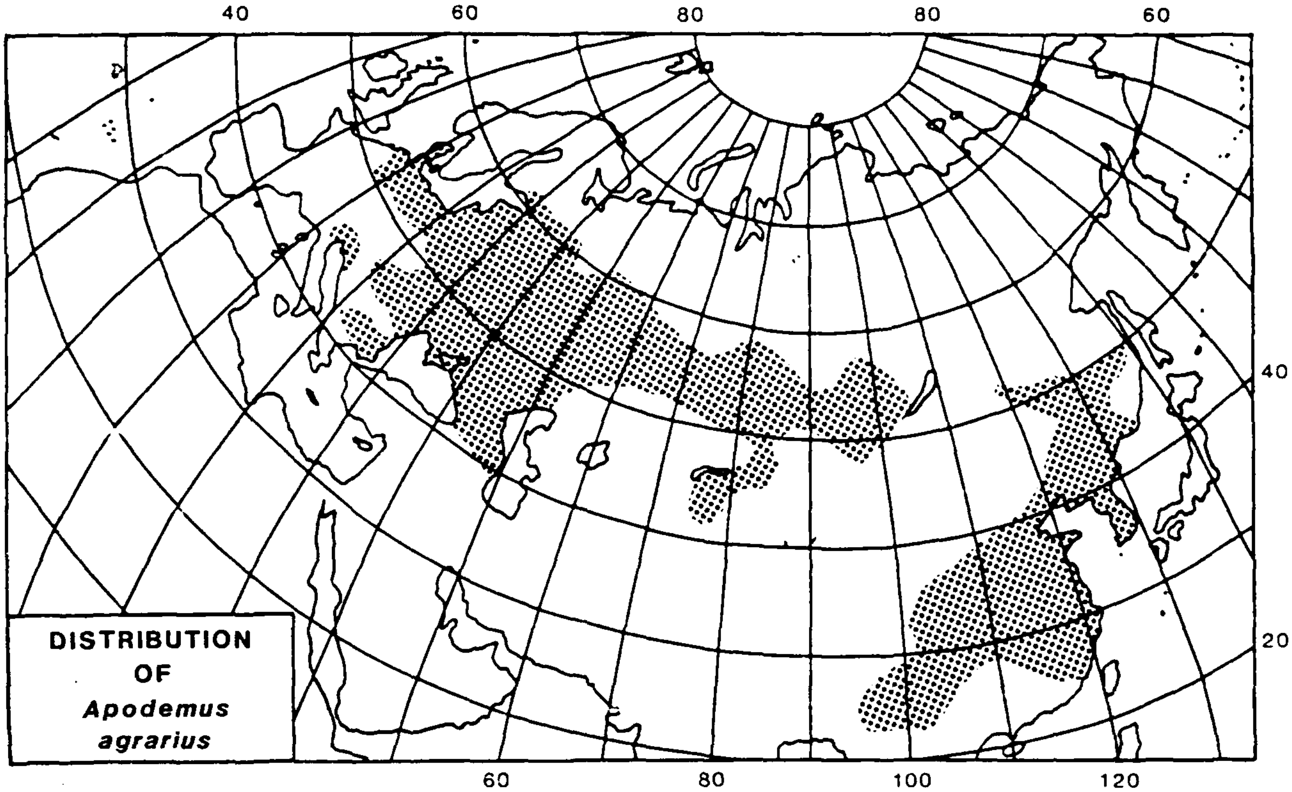

Figure 3 Geographical distribution of *Apodemus agrarius*, primary host of Hantaan virus. Reprinted from Corbet GB. *The Mammals of the Palaearctic Region: A Taxonomic Review*. Trustees of the British Museum (Natural History) 1978. Used by permission of the publisher, Cornell University Press.

mine if the viruses isolated from domestic rats captured in the United States were identical to Hantaan virus (23). As shown in Table 1, when these isolates were compared to prototype Hantaan virus by cross IFA assays, the viruses isolated from domestic rats captured in the U.S. were virtually identical to prototype Hantaan virus. When these same viruses and immune reagents were compared by cross plaque reduction neutralization tests, the urban rat viruses could be differentiated easily from prototype Hantaan virus (Table 2). The conclusion from these studies was that the viruses recovered from domestic rats in the United States were similar to prototype Hantaan virus, but clearly distinct from it.

Table 1 Comparison of U.S. domestic rat isolates with Hantaan virus by immunofluorescent antibody assay

	Virus		
Antibody	Hantaan	Philadelphia isolate	Houston isolate
HTN MHAF[a]	4096[b]	4096	4096
KHF[c] patient serum	512	512	512
Philadelphia isolate	8192	16384	8192
Houston isolate	1024	1024	2048
NE[d] patient serum	16384	[illegible]	8192

[a]Mouse hyperimmune ascitic fluids produced to prototype Hantaan virus, strain 76-118.
[b]Reciprocal of highest dilution giving characteristic cytoplasmic fluorescence; homologous reactions underlined.
[c]Korean hemorrhagic fever.
[d]Nephropathia epidemica.

Table 2 Comparison of U.S. domestic rat isolates with Hantaan virus by plaque reduction neutralization tests.

	Virus		
Antibody[a]	Hantaan	Philadelphia isolate	Houston isolate
HTN MHAF	10,240[b]	1280	640
KHF patient serum	2560	320	80
Philadelphia isolate	160	2560	1280
Houston isolate	40	5120	5120
NE patient serum	10	10	10

[a]Antibody as in Table 1.
[b]Reciprocal of highest dilution reducing 50% of plaque dose (100 pfu).

The global distribution of rat-associated Hantain-like viruses was addressed by examining rat sera from different areas of the world (2). Antibody positive rats were captured from most locations sampled around the world and several additional Hantaan-like virus isolations have been made (24–28). Positive rats were not limited to port facilities, but rather were found in many different habitats where rodent control programs were not adequate or nonexistent. Apparently the viruses found in domestic rats are unique and exist in nature completely independent of Hantaan virus. International shipping may have played a role in initially disseminating the virus, but that seems to have occurred some time in the past, since the virus now appears to be well established in domestic rats world-wide.

Childs, *et al.* (29) have attempted to investigate

Vol 37, No 4
Laboratory Animal Science
August 1987

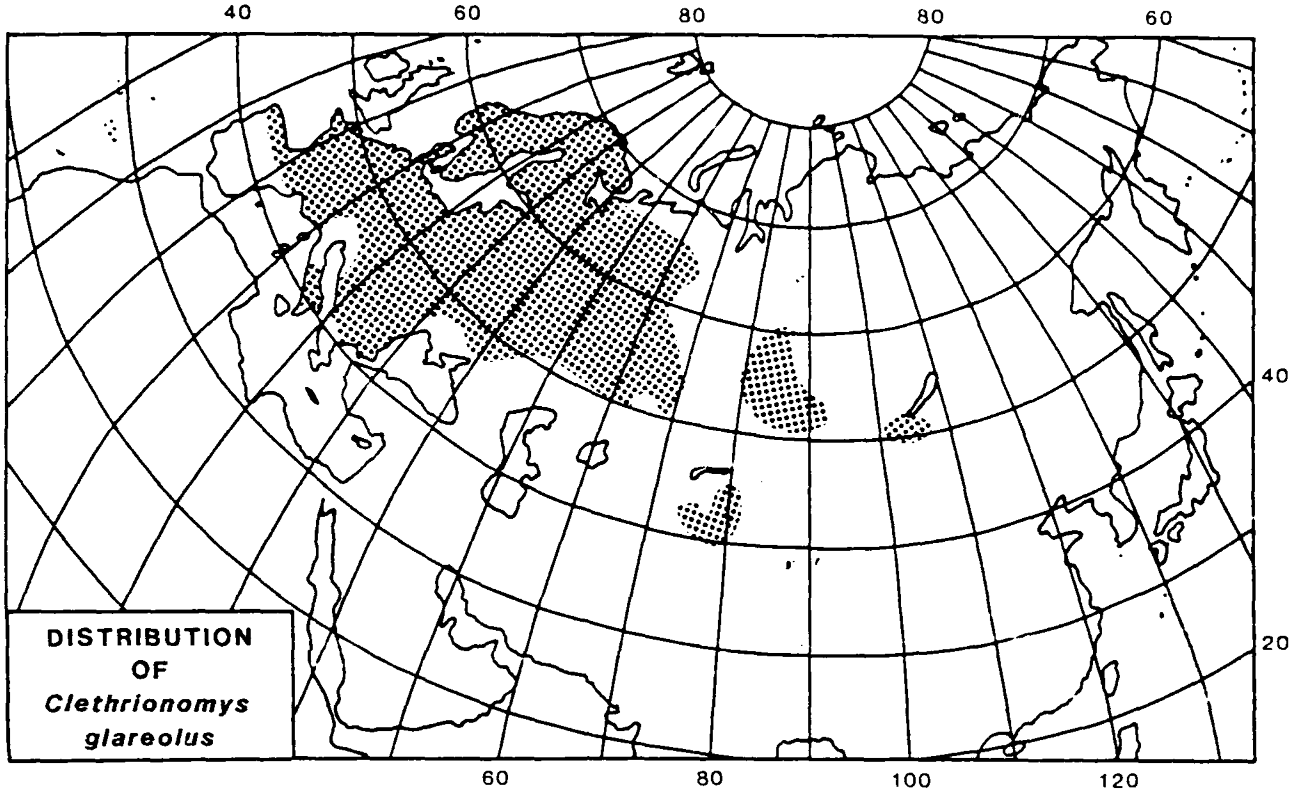

Figure 4 Geographical distribution of *Clethrionomys glareolus*, primary host of Puumala virus, etiologic agent of nephropathia epidemica. Reprinted from G.B. Corbet: *The Mammals of the Palaeractic Region: A Taxonomic Review*. Trustees of the British Museum (Natural History) 1978. Used by permission of the publisher, Cornell University Press.

in detail the ecology of Hantaan-like viruses and domestic rats in the urban setting. While their work is still in progress, they have made several interesting observations. For example, it is known that rat weight to approximately 400-500g is a valid estimator of age (30). When antibody titers of rats captured in Baltimore were plotted against their weight, rats which weighed less than 300 g generally lacked antibody, while those heavier and presumably older had a significant proportion which was antibody-positive. This suggests that Hantaan-like viruses may not be vertically transmitted, but rather are acquired horizontally at some time after weaning.

A mild form of HFRS has been attributed to Hantaan-like viruses associated with urban rats. Convincing studies, which describe HFRS following infection with urban rat-associated Hantaan-like viruses, have been published from both Korea (20) and China (25), and while the disease has yet to be documented in other areas, it seems likely that human illness may well be diagnosed elsewhere once clinical suspicion is sufficiently aroused and diagnostic tests become widely available.

HFRS in animal handlers and laboratory rats

A special situation has come to light which involves laboratory rats infected with Hantaan-like viruses. This problem was first reported by Umenai, *et al.* (31) when he described an outbreak of HFRS among animal handlers in Japan. Furtner study disclosed that the problem was not limited to a single institution, but rather was wide-spread among research facilities in both Japan (32-34) and Korea (35), and several persons were infected in these episodes. Cases were limited to persons either directly or indirectly exposed to laboratory animals, and in most instances, the source of the human disease could be traced back to infected laboratory rats. These observations were extended recently to include laboratory rat colonies in Europe as well, with a report of HFRS among animal caretakers in Belgium (15). Again, the source of infection was traced to infected laboratory rat colonies. Additional accounts recently have described outbreaks in laboratories in both France (14) and England (36).

Preliminary results indicate that most U.S. commercial animal breeders have eliminated Hantaan-like viruses in their animals through barrier breeding and ceasarean derivation. However, small suppliers and producers of select inbred strains may have not employed these breeding techniques and may be at risk of infection. Since rats appear to be asymptomatically infected, it is impossible to identify infected individuals without serological testing. Further, since the rats are infected chronically and shed the virus persistently, shipment of such

rats may inadvertently disseminate the agent. The problem is further compounded by the lack of a readily available diagnostic test to rule out infection. Development of such a test is needed desperately and a screening procedure must be instituted to assure that infected laboratory animals are not transported.

An additional concern was that rat-origin cell lines or rat-mouse hybridomas may be infected with Hantaan-like viruses, perhaps being distributed with Hantaan-like viruses as adventitious agents. In response to this concern, all cell lines of rat origin and all rat-mouse hybridomas held in the American Type Culture Collection were screened recently for the presence of Hantaan-like viruses and found to be negative (37). While this relieves immediate concern, the possibility that rodent-origin cell cultures might harbor Hantaan-related viruses remains a real threat.

Puumala virus, nephropathia epidemica, and *Clethrionomys glareolus*

Nephropathia epidemica (NE) is a relatively mild form of HFRS found in Scandinavia, the western Soviet Union, and much of Europe (38). Significant clinical symptoms include sudden onset, fever, abdominal or low back pain, serum creatinine elevation, and polyuria. While many patients are hospitalized during the acute phase, fatalities and permanent sequelae are rare. The disease is most often seen in adults, especially men, and is clearly associated with rural exposure (38,39). The bank vole, *Clethrionomys glareolus* is the natural host of the virus (40), and the distribution of NE probably corresponds closely to the distribution of this vole, as shown in Figure 4 (41). Infection in man is almost always traceable to contract with infected voles. Commonly, patients are infected when they occupy a summer cabin in which voles have nested, or clean out an infested barn or basement. The disease in Scandinavia is seasonal, with most cases occurring in the late fall and early winter, when infected voles seeking protection from the elements may invade man-made structures, and in mid to late summer, when people are most active outdoors (38,39). In addition, the populations of voles vary considerably. Vole populations in Scandinavia are often on a 4-year cycle, with peak numbers in one year, followed by a dramatic crash, then gradual build-up again to another peak about 4 years later. Population peaks throughout Scandinavia are not synchronous, so that different vole populations will peak during different years. As expected, cases of nephropathia epidemica are most common during peak populations of voles.

The isolation of the causative agent of nephropathia epidemica is a very recent advancement. Finnish workers detected antigen in the lungs of *Clethrionomys glaeolus*, demonstrated that the antigen reacted specifically with convalescent sera of NE patients, and proposed the name Puumala virus (40). However, they were not successful in propagating the virus, and it has only been recently that the virus has been adapted successfully to growth in cell culture (42-44). The virus has now been shown to be clearly distinct from prototype Hantaan virus and the Hantaan-like viruses from domestic rats (6,45,46).

Prospect Hill virus and *Microtus pennsylvanicus*

Prospect Hill virus is the most recent addition to the genus *Hantavirus*. It was isolated by workers at the National Institutes of Health from the meadow vole, *Microtus pennsylvanicus* (47). The first isolation was from a vole captured on Prospect Hill in Frederick, Maryland, thus the origin of the name for the virus. At present, no human disease has been attributed to infection with Prospect Hill virus, although antibody to the virus has been identified among mammalogists in the United States (48). A second host of the virus may be *Microtus californicus*, some of which have been identified with antibody to Prospect Hill virus. Serosurveys of small mammals captured in the United States suggest that the distribution of the virus is similar to the distribution of these species, which includes much of North America.

Epidemiology of hantaviruses

It should be apparent that the epidemiology of the hantaviruses is intimately linked to the ecology of their principle vertebrate hosts. Many, if not all, hantaviruses are capable of causing human disease, and in some cases, fatalities. Infection in man is a direct result of exposure to infected rodents themselves or to their infectious byproducts. As discussed, four distinct viruses are now recognized within the genus and that total is likely to increase as investigations continue. Similarly, it is quite likely that additional species of rodent hosts will be identified as significant to the maintenance of these viruses. In fact, many other species have been found with antibody to hantaviruses, and those discussed are only representatives of the better defined maintenance cycles. The contribution of other species is still to be determined. Clearly much work is needed before we fully understand this important group of viruses.

Acknowledgement

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